ligands on cells. The references state that PSGL-1 inhibitors can function to reduce leukocyte adherence, which in turn can reduce inflammation and inflammatory conditions. However, there is no disclosure in either reference that PSGL-1, or chimeric constructs comprising PSGL-1, can be used in conjunction with a surgical procedure to treat atherosclerosis or restenosis, as claimed in present claims 51, 52, 59, 73 and 74. Moreover, neither reference discloses that PSGL-1, or chimeric versions thereof, can be used for decreasing the formation or growth of lesions or plaques in the vessels of mammals.

Applicants reiterate and emphasize that neither restenosis nor atherosclerosis is an inflammatory condition such as the conditions addressed in the cited references. See pages 1, 2 and 5 of the present specification which describe the differences between atherosclerosis and events such as ischemia and reperfusion injuries. Also enclosed with this Amendment are extracted pages from Robbins, *Pathologic Basis of Disease,* pages 10 and 473 (1994). As shown in the Robbins citation, ischemia is caused by a lack of oxygen to tissues or organs, often due to a lack of blood flow to the tissues or organs. A reperfusion injury results from a restoration of the blood flow, and a resultant increase in toxic oxygen species in the organ or tissue. In contrast, atherosclerosis is a form of arteriosclerosis characterized by intimal thickening and lipid deposition, resulting in a thickening and loss of elasticity of the arterial walls.

The Tedder et al. reference relates to chimeric peptides or polypeptides that combine the ligand binding features of the domains of two different selectin molecules. The chimeric molecules of Tedder et al. are used to mediate leukocyte adhesion and function in the circulation system, and are thereby described as being useful as anti-inflammatory compounds. There is no disclosure in Tedder et al. that these chimeric molecules can be used to treat atherosclerosis or restenosis, or that these molecules can be used to reduce lesions or plaque.

Although the Examiner has grouped atherosclerosis and ischemia together as both involving a "platelet-leukocyte interaction", the prior art makes no such connection. See, for instance, pages 1 and 2 of the present specification which point out that atherosclerotic lesions are formed as a result of the binding of monocytes and T-lymphocytes to the surfaces of endothelial cells in the lumen of the artery wall. The monocytes become macrophages, accumulate lipids, and become foam cells. It is these cells, together with T-lymphocytes, that form lesions and fibrous plaques. This is distinct from the platelet-leukocyte interactions present in ischemia and reperfusion injuries.

The Examiner has cited the Coller et al. reference in an attempt to overcome the deficiencies of the Cummings et al. and Tedder et al. references. In particular, the Examiner states that Coller et al. teach the use of thrombolytic agents to prevent platelet aggregation and thrombosis which might otherwise occur as a result of angioplasty procedures. However, the present invention is directed to the prevention of atherosclerotic lesion formation in mammals, not the formation of a thrombosis. The prevention of thrombosis formation and the prevent of arterial plaque formation are two entirely different and unrelated clinical events as shown by the Robbins reference relied upon above. Accordingly, any combination of Coller et al. with the other references would still fail to teach or suggest the invention defined by the present claims.

In view of the foregoing facts and reasons, the present application is now believed to overcome the remaining rejections, and to be in proper condition for allowance. Entry of the foregoing amendment is deemed appropriate at this time since it only serves to correct typographical errors in two of the pending claims. Accordingly, reconsideration and withdrawal of the rejections, and favorable action on this application, is solicited. The Examiner is invited to contact the undersigned at the telephone number listed below to discuss any matter pertaining to this application.

Respectfully submitted,

by William G. Gosz

William G. Gosz
Reg. No. 27,787
Ropes & Gray
One International Place
Boston, MA
Attorneys for Applicant(s)
Tel. No. (617) 951-7000

Date: 10/24/02

MARKED-UP CLAIMS

73. (Three Times Amended) A method for treating [restinosis] restenosis in a mammal to which a vessel-corrective technique is administered comprising:

performing a vessel-corrective technique selected form the group consisting of angioplasty, stenting procedure, atherectomy, and bypass surgery on a mammal; and

administering to said mammal, prior to, in conjunction with or after said vessel-corrective technique, an effective amount of a soluble chimeric construct comprising P-selectin glycoprotein ligand-1 or a fragment thereof, and another molecule, said chimeric construct being capable of inhibiting the interaction between P-selectin and a ligand of P-selectin, such that the [restinosis] restenosis occurring after said vessel-corrective technique is thereby treated.

74. (Three Times Amended) A method for treating [restinosis] restenosis in a mammal, comprising:

providing a soluble chimeric construct comprising P-selectin glycoprotein ligand-1 or a fragment thereof and another molecule, said chimeric construct being capable of inhibiting the interaction between P-selectin and a ligand of P-selectin; and

administering to a mammal an effective amount of said chimeric construct such that said P-selectin-ligand interaction is inhibited, wherein said chimeric construct is administered prior to, in conjunction with, or after a vessel-corrective technique.

Robbins
PATHOLOGIC BASIS OF DISEASE

5th Edition

Ramzi S. Cotran, M.D.
Frank Burr Mallory Professor of Pathology
Harvard Medical School
Chairman, Departments of Pathology
Brigham and Women's Hospital
The Children's Hospital
Boston, Massachusetts

Vinay Kumar, M.D.
Vernie A. Stembridge Chair in Pathology
Southwestern Medical School
The University of Texas
Southwestern Medical School
Dallas, Texas

Stanley L. Robbins, M.D.
Visiting Professor of Pathology
Harvard Medical School
Senior Pathologist
Brigham and Women's Hospital
Boston, Massachusetts

Managing Editor

Frederick J. Schoen, M.D., Ph.D.
Associate Professor of Pathology
Harvard Medical School
Vice-Chairman, Department of Pathology
Brigham and Women's Hospital
Boston, Massachusetts

W.B. SAUNDERS COMPANY
A Division of Harcourt Brace & Company
Philadelphia London Toronto Montreal Sydney Tokyo

W.B. SAUNDERS COMPANY
A Division of
Harcourt Brace & Company

The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106

Library of Congress Cataloging-in-Publication Data

Cotran, Ramzi S.
Robbins pathologic basis of disease. —5th ed. / Ramzi S. Cotran, Stanley L. Robbins, Vinay Kumar.
p. cm.
Includes bibliographical references and index.
ISBN 0-7216-5032-5
1. Pathology. I. Robbins, Stanley L. (Stanley Leonard).
II. Kumar, Vinay. III. Title. IV. Title: Pathologic basis of disease.
[DNLM: 1. Pathology. QZ 4 C845r 1994]
RB111.R62 1994
616.07—dc20
DNLM/DLC 94-2629

Robbins Pathologic Basis of Disease, 5th edition ISBN 0-7216-5032-5

Copyright © 1994, 1989, 1984, 1979, 1974 by W.B. Saunders Company.

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher.

Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

injuries that pierce the walls of artery and vein and produce an artificial communication, or from inflammatory necrosis of adjacent vess ls. The connection between artery and vein may consist of a well-formed vess l, a vascular channel formed by the canalization of a thrombus, or an aneurysmal sac. Such lesions are rare and usually small. Nevertheless, they are often of clinical significance because they short-circuit blood from the arterial to the venous side, causing the heart to pump additional volume. This can induce cardiac failure (high-output failure). Moreover, they can rupture and cause hemorrhage, especially in the brain. In contrast, intentionally created AV fistulas are used to provide vascular access for chronic hemodialysis.

ATHEROSCLEROSIS AND OTHER FORMS OF ARTERIOSCLEROSIS

Arteriosclerosis literally means "hardening of the arteries"; more accurately, however, it refers to a group of disorders that have in common thickening and loss of elasticity of arterial walls. Three distinctive morphologic variants are included within the term arteriosclerosis: *atherosclerosis*, characterized by intimal thickening and lipid deposition; *Monckeberg's medial calcific sclerosis*, characterized by calcification of the media of muscular arteries; and *arteriolosclerosis*, marked by proliferative or hyaline thickening of the walls of small arteries and arterioles. Because atherosclerosis is by far the most common and important form of arteriosclerosis, it is discussed first and in detail.

ATHEROSCLEROSIS

Atherosclerosis overwhelmingly accounts for more death and serious morbidity in the Western world than any other disorder. Global in distribution, it has reached epidemic proportions in economically developed societies. Although any artery may be affected, the aorta and the coronary and cerebral systems are the prime targets, and so *myocardial infarction, cerebral infarction, and aortic aneurysms* are the major consequences of this disease. Atherosclerosis also takes a toll through other consequences of acutely or chronically diminished arterial perfusion, such as *gangrene of the legs, mesenteric occlusion, sudden cardiac death, chronic ischemic heart disease*, and *ischemic encephalopathy*. Despite a reduction in mortality from myocardial infarction and other forms of ischemic heart disease, nearly 50% of all deaths in the United States continue to b attributed to atherosclerosis-related diseases. Although not usually clinically evident until middle age or later, when the arterial lesions precipitate organ injury (Fig. 11–4), atherosclerosis is a slowly progressiv disease that begins in childhood.[8]

DEFINITION. Atherosclerosis is a disease primarily of the elastic arteries (e.g., aorta, carotid, and iliac arteries) and large and medium-sized muscular arteries (e.g., coronary and popliteal arteries). *The basic lesion—the atheroma, or fibrofatty plaque—consists of a raised focal plaque within the intima, having a core of lipid (mainly cholesterol and cholesterol esters) and a covering fibrous cap.* Atheromas are sparsely distributed at first, but as the disease advances, they become more and more numerous, sometimes covering the entire circumference of severely affected arteries. As the plaques increase in size, they progressively encroach on the lumen of the artery as well as on the subjacent media. *Consequently, in small arteries, atheromas are occlusive, compromising blood flow to distal organs and causing ischemic injury, but in large arteries they are destructive, weakening the affected vessel wall, causing aneurysms or rupture, or favoring thrombosis. Moreover, extensive atheromas are friable, often yielding emboli of their grumous contents into the distal circulation (atheroemboli), most commonly noted in the kidneys.*

EPIDEMIOLOGY AND RISK FACTORS. The variable occurrence and severity of atherosclerosis among individuals and groups may provide important clues to its pathogenesis. Epidemiologic data are expressed largely in terms of the *incidence of or the number of deaths caused by ischemic heart disease (IHD)* (see Chapter 12).

Deaths from cardiovascular disease in the United States rose from 14% of all deaths in 1937 to 54% in 1968, almost all cases being related to atherosclerosis. Happily, they appeared to plateau in the late 1960s, and by 1975, for the first time, the rate showed a statistically significant decline, which has been maintained since. The downward trend is believed to be mediated largely by a reduction in atherosclerosis influenced by changes in diet and lifestyle, better control of hypertension, and improved therapy for myocardial infarction and other complications of IHD.

Nevertheless, the death rate related to atherosclerosis in the United States is still among the highest in the world, lower than for Finland and Scotland, but above that of other well-developed, affluent countries, such as Canada, France, and the other Scandinavian countries. The rates are remarkably low in Asia, Africa, and South and Central America. For example, death rates from IHD in Japan are one-sixth of those in the United States. Japanese who migrate to the United States, how-

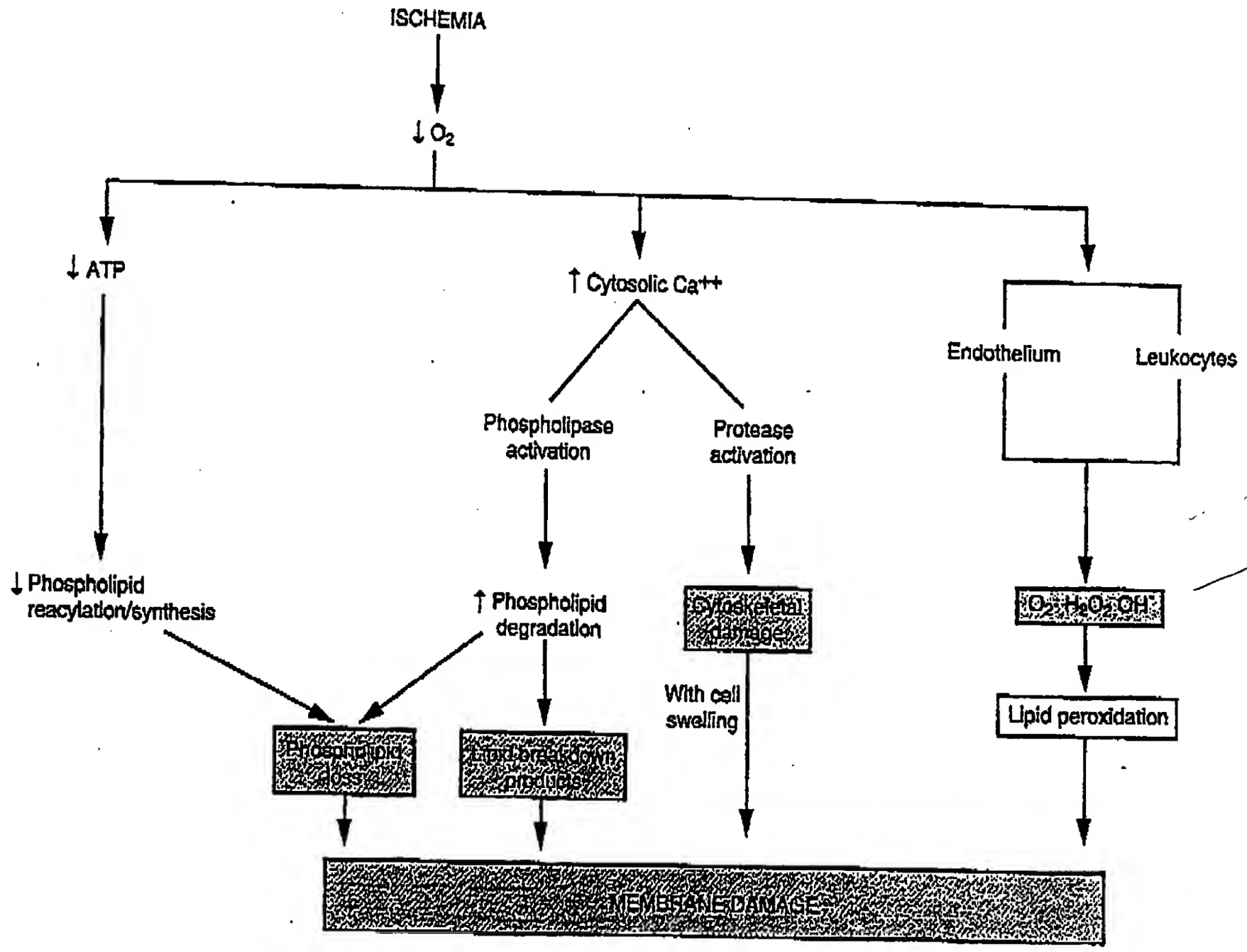

Figure 1–7. Mechanisms of membrane damage in ischemia. *(See text.)*

membranes and other cell constituents. Such free radicals are present at very low levels in myocardium during ischemia, but there is an increase in free radical production *on restoration of blood flow*. Reperfusion results in a paradoxic effect: an *increase* in damage called *reperfusion injury*. This injury can be reduced by antioxidants in some models of ischemia. Although reactive oxygen species in postischemic tissue can be derived from incomplete reduction of oxygen by mitochondria and production of superoxide ion by xanthine oxidase (from vascular endothelium), it is thought that most toxic oxygen species are *produced by polymorphonuclear leukocytes that infiltrate the site of ischemia during reperfusion*.[13] It must be emphasized that if reperfusion does not occur, lethal ischemic cell injury still eventually ensues, but toxic oxygen species are probably not involved under these conditions.

4. *Lipid breakdown products.* These include unesterified free fatty acids, acyl carnitine, and lysophospholipids, catabolic products that are known to accumulate in ischemic cells as a result of phospholipid degradation. They have a detergent effect n membranes. They also either insert into the lipid bilayer of the membrane r exchange with membrane ph spholipids, potentially causing changes in permeability and electrophysiologic alterations.

5. *Loss of intracellular amino acids.* Addition of certain amino acids, principally glycine and L-alanine, protects hypoxic cells from irreversible membrane damage *in vitro*, suggesting that loss of such amino acids—which occurs in hypoxia—predisposes to membrane structural injury.[15] The mechanisms of protection by glycine are, however, unclear.

Whatever the mechanism(s) of membrane injury, the resultant loss of membrane integrity causes further influx of calcium from the extracellular space. When, in addition, the ischemic tissue is reperfused to some extent, as may occur *in vivo*, the scene is set for massive influx of calcium. Calcium is taken up avidly by mitochondria after reoxygenation and permanently poisons them, inhibits cellular enzymes, denatures proteins, and causes the cytologic alterations characteristic of coagulative necrosis.[16]

It is evident that the molecular events that determine irreversible cell damage are complex. Inde d, it is likely that several mechanisms, acting at more than one locus, underli cell death. *For now it must suffice to say that hypoxia affects oxi-*